UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,248	05/06/2002	Peter D. Davis	U 013864-1	8432

140 7590 12/27/2005

LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,248	DAVIS, PETER D.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,13,14,20,21,25-27,29,30 and 33-45* is/are pending in the application.

4a) Of the above claim(s) *10,14 and 37-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 13, 20, 21, 25-27, 29, 30 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-10, 13, 14, 20, 21, 25-27, 29, 30 and 33-45 are currently pending in the instant application. Claims 10, 14 and 37-45 are withdrawn from consideration as being for non-elected subject matter and claims 1, 4-9, 13, 20, 21, 25, 26, 27, 29, 30 and 33-36 are rejected.

Response to Amendment and Arguments

Applicants' amendment filed 27 September 2005 has overcome the objection of claim 8 as claim 28 has been cancelled. The 35 USC 103(a) rejections of claims 1, 4-9, 13, 20, 21, 25, 26, 27, 29, 30 and 33-36 are maintained. In regards to the 35 USC 103(a) rejections, applicants' arguments filed 27 September 2005 have been fully considered but they are not persuasive. Applicant argues that the Declaration under 37 CFR 1.132 signed by the inventor, filed 27 August 2004 is now commensurate in scope with the claims, as the claims have been amended. Furthermore, applicant argues that according to MPEP section 716.02(d), the nonobviousness of a broader claim limitation can be supported by evidence based on unexpected results from testing a species if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. However, this argument is not considered persuasive as the declaration only compares one compound from applicants' instantly claimed genus of compounds including salts, solvates, hydrates and prodrugs thereof. Therefore, applicant has not compared the instantly claimed invention (which comprises many more compounds than have been instantly compared to the prior art). While applicant argues that MPEP 716.02(d)

supports that the declaration filed is commensurate in scope with applicants' claimed invention, it is noted that MPEP 716.02(d) states :

> The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof.

Applicants' declaration on filed does not test a narrower range, but only provides tests for one compound, therefore one of ordinary skill in the art would not be able to determine a trend as there is only one compound of the claimed invention tested in the declaration. as stated on page 3 of the previous action, applicant has not compared the invention with the closest prior art which is combretastatin A-4, see lines 2 and 11 of the previous action.

Applicant also argues that the declaration filed 27 August 2004 shows unexpected results and does not just work as intended. Applicant cites MPEP 716.02(a) for support. Applicants' argument is not persuasive as first it is pointed out as stated on page 3 of the previous action, applicant has not compared the invention with the closest prior art which is combretastatin A-4, see lines 2 and 11 of the previous action. Secondly, while applicant has shown a difference in results, applicant has not provided a showing as stated in MPEP 716.02(a) and (b) that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Specifically, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. The evidence relied upon does not discuss how or provide a showing that the differences in results are in fact

unexpected and unobvious and of both statistical and practical significance. Applicant has the burden of explaining the data in any declaration they proffer as evidence of non-obvoiusness. The declaration filed 27 August 2004 does not explain the data nor does it show that the results are of a significant, practical advantage. Applicant has failed to provide a showing of sufficient scope, and failed to further show that the results are greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. (reference AT on form 1449).

Applicant's instant claims 1 and 4 are drawn towards a cis-stilbene of formula (I) (claim 1) wherein R1, R2, R3 can be methyl and R5 is hydrogen. Claim 4 is drawn to the specific compound (Z) –1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane.

Determining the scope and contents of the prior art

The prior art reference of Woods et al. discloses Combretastatin A-4, figure 1, page 705, which interacts with tubulin with resultant disruption of microtubular function. Page 709 of Woods et al. discloses that the 4'methoxy and 3'hydroxy groups of combretastatin A-4 are not essential for the interaction with tubulin. Furthermore, page 710 of Woods et al. discloses Figure 8 which shows that small alkyl groups at a position equivalent to applicant's R4 do not adversely affect activity of the compound and methoxy is not essential at this position. Page 710 discloses that the interaction with tubulin is tolerant of the replacement of the 4'-methoxy by methyl or ethyl, and also, (e) of page 710 discloses that the replacement of the 4'methoxy group of combretastatin A-4 can be replaced with small hydrophobic groups while still retaining significant activity against tubulin

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art reference and the claims at issue is that in the position equivalent to applicant's R4 substituent, the prior art reference contains a methoxy group, which is not a variable included in applicant's instant claims.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art at the time of the invention to prepare compounds of

applicant's instant claim 1, which have vascular damaging activity, including compounds of applicants instant claim 1 wherein R1, R2, and R3 are methyl, R4 is methyl and R5 is hydrogen when faced with combretastatin A4 in the prior art reference of Woods et al. The motivation is provided in the prior art reference by the disclosure that small alkyl groups at the 4' position do not adversely affect activity of the compound, that methoxy is not essential at the 4' position, that the interaction with tubulin is tolerant of the replacement of the 4'methoxy with methyl or ethyl and that the 4'methoxy can be replaced with small hydrophobic groups while still retaining significant activity against tubulin. The disclosure by Woods et al. that the 4'metoxy group is not necessary and that the replacement of the 4'-methoxy by a small alkyl group or small hydrophobic group would not adversely affect the activity of the compound would motivate someone of ordinary skill in the art to prepare compounds as instantly claimed by applicant in order to have more compounds which are useful for the disruption of microtubular function and for the treatment of tumors.

Claims 5-9, 13, 20, 21, 25-27, 29, 30 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. as applied to claims 1-4 above, and further in view of WO 92/16486 or WO 99/35150.

Applicants instant claims 5-9, 13, 20, 21, 25-27, 29, 30 and 33-36 are drawn towards prodrugs of the compound of formula (I), specifically phosphate esters of the compound of formula (I) and compositions of the compound of formula (I).

Determining the scope and contents of the prior art

WO/92/16486 discloses compounds which have greater aqueous solubility than Combretastatin A4 and exhibit greater stability, which are prodrugs such as the compound of formula (I) (page 2) wherein Y is a phosphate or a phosphate derivative, the prodrug of the phosphate derivative is particulary preferred (page 3). These compounds can be dissolved in a phosphate buffered saline (page 20) for the preparation of a pharmaceutical formulation of the compound.

WO 99/35150 discloses combretastatin A4 prodrugs, of which phosphate salts are the most stable and suitable (page 6). Page 7 discloses phosphate ester prodrugs which are water soluble. These compounds can be added to a sterile vehicle such as water to be administered as a pharmaceutical composition (page 36).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art of WO 92/16486 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

The difference between the prior art of WO 99/35150 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art to prepare phosphate ester prodrugs of the compound as found in applicants instant claim 1 and to prepare pharmaceutical compositions when faced with the prior art reference of Woods at al. and one of WO 92/16486 or WO 99/35150 since Woods et al. discloses that the 4'methoxy of Combretastatin A-4 can be replaced by a small alkyl group or a small hydrophobic group without causing an adverse reaction in activity and Wo 92/16486 or WO 99/35150 disclose the phosphate ester prodrugs of Combretastatin A4 and disclose that these phosphate esters have improved aqueous solubility and characteristics for use as a prodrug in pharmaceutical formulations. One of ordinary skill in the art would be motivated to prepare prodrugs of the formula as instantly claimed by applicant and to prepare pharmaceutical compositions by the prior art references to prepare other useful compounds which interact with tubulin and are useful in the treatment of cancer.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for

Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600